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Non-contrast CT attenuation value of renal papilla is a novel predictor of recurrence in kidney stone disease

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Abstract

In calcium stone formers, most stones grow attached to Randall's plaque, which can be identified by measuring the computed tomography (CT) attenuation value of renal papilla. We hypothesized that the CT attenuation value of renal papilla can predict the severity (recurrent or multiple stone former) and recurrence of the stone disease. We retrospectively reviewed the charts of 180 calcium oxalate stone formers who underwent non-contrast CT and 24-hour urine chemistry in our hospital between September 2012 and November 2021. Two observers independently measured the Hounsfield unit (HU) of the renal papilla and classified the patients into the low-HU and the high-HU value groups according to the median value (38.9 HU). The proportion of recurrent and multiple stone formers were similar between the low-HU group and the high-HU group (70.0% vs. 65.6%, 71.1% vs. 74.2%, respectively). There were also no significant differences in urinary volume, urinary excretions of each constituent, or AP(CaOx) index between the two groups. On the other hand, the recurrence rate in the high-HU value group (0.10 events/person/year) was significantly higher than that in the low-HU value group (0 events/person/year, $p=0.03$). Multivariate analysis revealed that high-HU value was an independent predictor of stone recurrence (OR 1.90, 95% CI 1.00-3.64, $p=0.04$) as well as medical prophylaxis. The results of this study suggest that HU value of renal papilla is a useful predictor of recurrence of stone disease.

Keywords Nephrolithiasis, CT attenuation value, Renal papillae, Randall's plaque, AP index

Introduction

The European Association of Urology guidelines on urolithiasis recommend risk-stratified strategy in metabolic evaluation and recurrence prevention. Low risk stone forming patients are to be managed with general preventive measures, such as fluid intake and dietary advice. Meanwhile, for high risk stone forming patients, specific metabolic evaluation including 24-hour urine chemistry and stone-specific recurrence prevention including pharmacological therapy are recommended. Patients are considered to be at high risk if they have general risk factors (early onset of urolithiasis, familial stone formation), specific stone compositions or endocrine/metabolic/genetic/anatomical disorders associated with stone formation. Specific metabolic evaluation including 24-hr urine chemistry is necessary to appropriately assess the risk of stone recurrence. However, such metabolic evaluation is complicated and can be burdensome for patients. A novel, simple and effective tool to predict the risk of stone recurrence without the need for metabolic evaluation is therefore desired.

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In 2008, Eisner et al. first reported that the computed tomography (CT) attenuation values of renal papilla in 17 patients with stones were significantly higher than the values in non-stone-forming controls [1]. A later study demonstrated that CT values of renal papilla in the stone-bearing kidney and in the contralateral kidney in 90 patients with stones were significantly higher than those in non-stone forming controls [2]. These findings are consistent with the observation that many patients with nephrolithiasis also have Randall's plaques, which are hypothesized to be a nidus for stone formation [3].

We hypothesized that CT attenuation value of renal papilla can predict the severity and recurrence of stone disease in calcium oxalate (CaOx) stone formers. The present study aims to test this hypothesis.

Methods

Participants

We retrospectively reviewed the charts of CaOx stone formers who underwent non-contrast CT scans and 24-hour urine chemistry between September 2012 and November 2021 at Wakayama Medical University Hospital, Japan, and who were followed up for at least 1 year. Stone analysis was performed by infrared spectroscopy. Ideally, CaOx stones should be subdivided into CaOx monohydrate and CaOx dihydrate. Unfortunately, there are no Japanese laboratories that report CaOx monohydrate and CaOx dihydrate separately, so in this study, the two were combined and analyzed as CaOx. We excluded patients with radiolucent stones, with pure calcium phosphate stones, and with non-calcium stones. This study was approved by the Wakayama Medical University Institutional Review Board (No. 3037) and all procedures were performed in accordance with the tenets of the Declaration of Helsinki. Since this is a retrospective observational study, clinical trial number is not applicable.

Measurement of CT attenuation value of renal papilla

CT scans were performed as standard with 5 mm collimation width using a LightSpeed 64-slice multidetector helical CT scanner at 0.5 s per rotation, 120 kV and 100 mA. CT images (slice thickness 2.5–5 mm) were retrospectively reviewed by two experienced urologists that were blinded to patient clinical data. The Hounsfield unit (HU) of the renal papilla was independently measured by two observers by placing regions of interest (ROI) with a mean size 0.2 cm^2 in the region of renal papillae from the upper pole, middle region and lower pole in both kidneys (Fig. 1a). Regions of interest were not placed on the small calcified lesions or calyceal stones (Fig. 1b). Mean CT values of all papillae were recorded for each patient. The reliability of the two independent observers' measurements was judged to be good, as the intraclass correlation coefficient (ICC) was measured to be 0.987.

Outcomes

We collected the following demographic and clinical data: age, gender, history of urinary stone disease, number of kidney stones, and the use of medical prophylaxis for stone disease. When available, laboratory data within 1 year before or after CT examination were also collected: 24-hour urine collection for volume, oxalate, calcium, uric acid, magnesium, citrate and biochemical analysis of stone material. The ion activity product of calcium oxalate (AP[CaOx]) as a risk index of calcium oxalate stone formation was calculated as follows: AP(CaOx) index = $1.9 \times Ca^{0.84} \times Ox^{1.0} \times Mg^{-0.12} \times Cit^{-0.22} \times V^{-1.03}$. Stone analysis was performed by Fourier transform infrared spectroscopy. A stone was considered to be pure CaOx if > 95% of its weight was comprised of the constituent. A stone was considered to be a non-calcium stone and was excluded from the study if there was detection of even a small amount of non-calcium constituents within it. All patients were regularly followed every 6 months with kidney, ureter and bladder radiography and

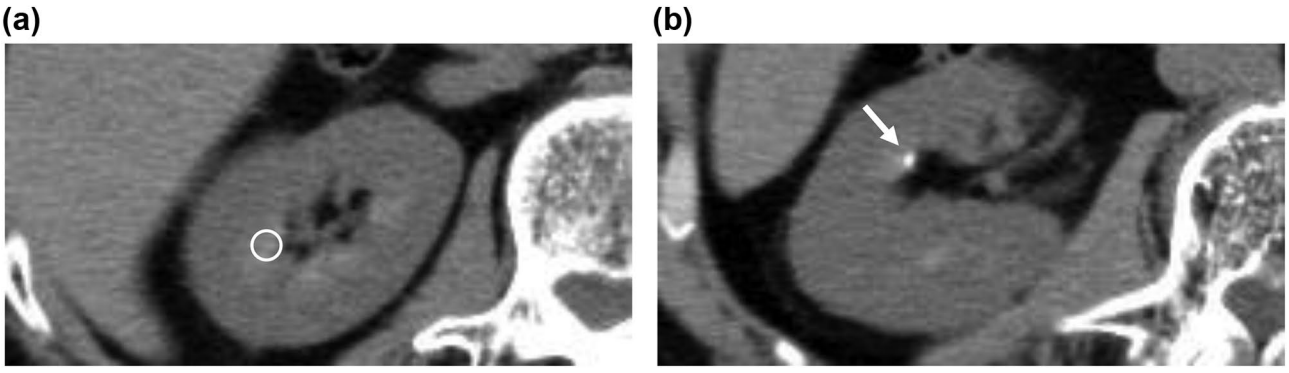

Fig. 1 Measurement of renal Hounsfield unit values. **(a)** The Hounsfield unit of the renal papilla was measured by placing regions of interest (circle) with a mean size 0.2 cm^2 in the region of renal papillae from the upper pole, middle region and lower pole in both kidneys. **(b)** The region of interest was not placed on small calcified lesions or calyceal stones (arrow)

ultrasound. When recurrence of stones was suspected or when recurrence was evident and the need for treatment was recognized, non-contrast CT scan was performed as an additional step. Stone recurrence was defined as new occurrence or growth of stones on regular imaging studies, stone-related symptoms and/or the need for intervention. Stone recurrence rate was calculated as the number of stone recurrence events per person per year.

Statistical analysis

Patients were classified into high-HU and low-HU value groups by the overall patient median CT attenuation value. We compared the proportions of recurrent stone formers and multiple stone formers, urine chemistries and recurrence rates between the groups. Continuous variables were expressed as median with interquartile range (IQR) and were analyzed using Mann-Whitney U test. Categorical variables were compared using the Chi square test. Logistic regression analysis was performed to define factors that affected stone recurrence. A two-sided p value <0.05 was considered to represent statistically significant differences. All statistical analyses were performed with JMP Pro 14.1.0. (SAS Institute, Cary, NC, USA)

Results

A total of 180 patients (114 men, 66 women) were included in the analysis. Baseline clinical characteristics are presented in Table 1. Stone composition was CaOx in 88 patients (48.9%), CaOx+CaP in 59 patients (32.8%) and unknown in 33 patients (18.3%). Recurrent stone formers and multiple stone formers accounted for 67.8% and 72.6% of the cohort, respectively. Median HU value of all papillae was 38.9, which was used for classification of the patients into either the low-HU group (<38.9) or high-HU group (≥38.9). There was no significant difference in the variability of the data between the High HU group and the Low HU group.

There were no significant differences in age, gender or stone composition between the two groups (Table 1). The proportions of recurrent stone formers and multiple stone formers were also similar between the groups (70.0% vs. 65.6%, 71.1% vs. 74.2%, respectively, Table 1).

Data on 24-h urine collection and AP(CaOx) index are shown in Table 2. Five patients (three in the low-HU group and two in the high-HU group) were excluded from the analysis because they lacked one of the items necessary for the calculation of AP (CaOx) index. There were no significant differences in urinary volume, urinary excretions of each constituent, or AP(CaOx) index between the low-HU and the high-HU groups.

Patients in the low-HU group and those in the high-HU group were followed for 3.5 years (interquartile range 2.6–5.1) and 4.0 years (interquartile range 3.0–6.5), respectively ($p=0.13$, Table 3). During the follow-up, 50.0% of patients in the high-HU group had at least one stone recurrence event, which was significantly higher than the 34.4% in the low-HU group ($p=0.03$). Stone recurrence rate in the high-HU value group was significantly higher than that of the low-HU value group (0.10 events/person/year [IQR 0–0.45] vs. no events/person/year [IQR 0–0.27], $p=0.03$, Table 3). Multivariable logistic regression model revealed that high-HU value was an independent predictor of stone recurrence (odds ratio [OR] 1.90, 95% CI 1.00–3.64, $p=0.04$) as well as the use of medical prophylaxis (OR 3.01, 95% CI 1.23–7.35, $p=0.01$, Table 4).

Discussion

The mechanism of CaOx stone formation is not yet completely clear, but Randall's plaque theory is the main hypothesis of stone formation [3]. Randall's plaque is

Table 1 Patient characteristics

	Total	Low-HU group (<38.9)	High-HU group (≥38.9)	p=
No. patients	180	90	90	
Age, year	58.5 (49 - 66)	61 (50 - 68)	57 (48 - 65)	0.12
Male , n (%)	114 (63.3)	56 (62.2)	58 (64.4)	0.75
Stone composition, n (%)				0.22
CaOx	88 (48.9)	47 (52.2)	41 (45.6)	
CaOx+CaP	59 (32.8)	31 (34.4)	28 (31.1)	
Unknown	33 (18.3)	12 (13.3)	21 (23.3)	
Recurrent stone former, n (%)	122 (67.8)	63 (70.0)	59 (65.6)	0.52
Multiple stone former, n (%)	130 (72.6)	64 (71.1)	66 (74.2)	0.64
CT value of renal papilla, HU	38.9 (35.0 – 43.2)	35 (31.8 – 37.3)	43.2 (41.0 – 46.2)	<0.01

Table 2 24-hour urine collection and ion activity product of calcium oxalate (AP[CaOx])

	Low-HU group (n=87)		High-HU group (n=88)		p=
Volume, mL/day	1627	(1297 - 2043)	1524	(1161 - 1882)	0.17
Oxalate, mg/day	26	(20 - 33)	26	(19 - 33)	0.70
Calcium, mg/day	184	(117 - 246)	173	(90 - 247)	0.52
Uric acid, mg/day	530	(396 - 647)	505	(390 - 636)	0.47
Magnesium, mg/day	74	(54 - 93)	70	(50 - 100)	0.60
Citrate, mg/day	379	(255 – 578)	350	(230 - 540)	0.30
AP(CaOx)	0.66	(0.47 – 0.86)	0.73	(0.47 – 0.95)	0.47

Table 3 Stone recurrence in low-HU group and high-HU group

	Low-HU group		High-HU group		p=
No. patients	90		90		
Follow-up, years	3.5	(2.6 – 5.1)	4.0	(3.0 – 6.5)	0.13
No. patients with recurrence (%)	31	(34.4)	45	(50.0)	0.03
No. recurrence /year	0	(0 - 0.27)	0.10	(0 - 0.45)	0.03

Table 4 Multivariable logistic regression model for stone recurrence

	Odds ratio	95% CI	p=
Age, years	0.97	0.95 - 1.00	0.08
Male	0.76	0.38 - 1.51	0.44
Multiple stone former	3.61	1.60 - 8.14	<0.01
Recurrent stone former	1.68	0.81 - 3.49	0.16
Medical prophylaxis	3.01	1.23 - 7.35	0.01
High-HU (≥38.9)	1.90	1.00 - 3.64	0.04

defined as calcium phosphate deposits lying under the papillary epithelium which may serve as a nidus for CaOx deposition and eventual stone formation. Increased excretion of urinary calcium, phosphate, and oxalate as well as decreased excretion of citrate is thought to contribute to intra-tubular crystal formation. However, the exact mechanism behind interstitial crystal formation and subsequent stone formation remains unclear [4].

Randall's plaque has been extensively histopathologically investigated in patients who underwent percutaneous nephrolithotomy [3, 5]. Following histological analysis of Randall's plaque, the next step was to show that calcification of the renal papillary area observed by endoscopy is a risk factor for stone recurrence [6]. However, this method requires an invasive examination. A study followed to determine whether CT values of the renal papillary region could be predicted for stone recurrence by simple CT. Several authors have therefore attempted to measure the HU of renal papillae by means of unenhanced CT with the hypothesis that localized calcifications such as Randall's plaque increase the radiologic density of tissues. In 2008, Eisner et al. first reported that the CT attenuation value of renal papilla in 17 patients with stones was significantly higher than that in non-stone-forming controls [1]. A later study also demonstrated that CT values of renal papilla in the stone-bearing kidney and in the contralateral kidney in 90 patients with stones were significantly higher than those in non-stone forming controls [2]. Interestingly, these two studies showed that the CT attenuation values of the renal papilla in patients with calculi were higher than those in all renal papillae in healthy subjects, regardless of the presence or absence of calculi, the healthy side, or the affected side. These results not only support that Randall's plaque can be detected as higher CT attenuation values, they also imply that Randall's plaque is formed by systemic rather than by local changes.

Ciudin et al. reported the clinical significance of CT attenuation value of renal papillae [7–10]. CT values of renal papillae in patients with calcium stones were higher than those in healthy subjects, but they were also higher on CT before the development of stones [8]. High CT attenuation values were demonstrated to not be the result of calcium stone formation, but rather they represent the cause of calcium stones, which supports Randall's plaque theory. They also followed up 187 patients who were treated for calcium stones and found to be stone free and found that renal papillary CT values were significantly higher in patients with recurrent stones than in those without recurrence [10].

In the current study, we focused on only calcium oxalate stone formers and divided them into two groups according to the CT attenuation value of real papillae: the low-HU group (<38.9) and the high-HU group (≥38.9). We wanted to ascertain whether the CT attenuation value is associated with the clinical course of patients with calcium stones. Although the HU value of renal papillae was not correlated with disease severity (multiple stone formers), recurrence rate in the high-HU value group was significantly higher than that of the low-HU value group (0.10 events/person/year [IQR 0–0.45] vs. 0 events/person/year [IQR 0–0.27], $p=0.03$). Multivariable logistic regression model revealed that high-HU value was an independent predictor of stone recurrence (odds ratio [OR] 1.90, 95% CI 1.00–3.64, $p=0.04$) as well as medical prophylaxis (OR 3.01, 95% CI 1.23–7.35, $p=0.01$). The results that the use of medical prophylaxes had a positive impact on stone recurrence might be because they are applied to patients who were thought to be at higher risk of recurrence.

Another unique feature of our study was the relationship between renal papillary CT values and 24-hour urine chemistries. Although only one previous study reported the relationship between renal papillae CT attenuation values and 24-hour urine chemistry [11], there was no correlation between papillary density and hypercalciuria. We also found no significant difference in daily urinary calcium excretion or AP (CaOx) index between the high and low renal papillary CT groups.

There are several limitations in regard to our study. First, the number of patients was small, and more patients are required to reach a stronger conclusion. Second, we targeted only patients with calcium stones, and many previous studies have examined not only patients with calcium stones, but also healthy controls. Third follow up period was rather short (3.5–4.0 years). Longer term observations will yield more accurate results.

However, our study showed that measurement of HU of renal papillae is useful for not only screening of future stone patients within the general public, but also in the establishment of follow-up plans for present patients with stones after treatment.

Conclusions

In conclusion, HU value of renal papilla correlated with recurrence in calcium oxalate stone formers in our cohort. HU value of renal papilla may be a simple and effective means of identifying patients with a higher risk of recurrent stone formations and facilitating change of clinical management for these patients.

Abbreviations

CT	Computed tomography
HU	Hounsfield unit
CaOx	Calcium oxalate
ROI	Regions of interest
IQR	Interquartile range

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Author contributions

Y.K. designed and conceived the project. S.Y. analyzed the data. Y.I. collected clinical data. R.D. performed statistical analysis. T.W. contributed the main text. I.H. wrote this manuscript.

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Data availability

The data of this study are available on request from the corresponding author.

Declarations

Ethics approval and consent to participate

This study was approved by Wakayama Medical University Ethical Committee (No. 3037). Since this study was a retrospective observational study, we published the research details on our website and gave subjects the opportunity to opt out, in accordance with Japanese ethical guidelines. Thus, informed consent to participate was obtained from all of the participants in this study.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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